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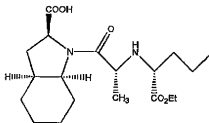
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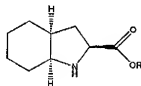
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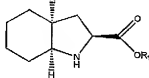
(54) Title: PROCESS AND PRODUCT



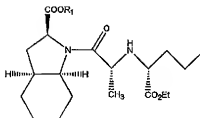
(I)



(II)



(III)



(IV)

(57) Abstract: A process of preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof which process comprises protecting a compound of formula (II) where R denotes a hydrogen atom, in the presence of benzene sulphonic acid as a catalyst, to obtain the benzene sulphonic acid salt of an ester of formula (III) where R₁ is a carboxyl protecting group and reacting said ester of formula (III) with N-[(S)-1-carboxybutyl]-[S]-alanine to obtain a compound of formula (IV) where R₁ is as defined above; and deprotecting a compound of formula (IV) to yield perindopril of formula (I), or a pharmaceutically acceptable salt thereof. There is also provided by the present invention the benzene sulphonic acid salt of an ester of formula (III), and perindopril or a pharmaceutically acceptable salt thereof prepared by the above process.

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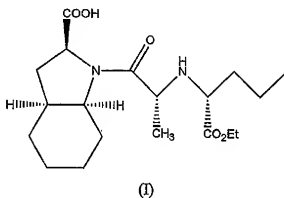


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PROCESS AND PRODUCT

The present invention relates to a novel process for the industrial synthesis of perindopril. More particularly, the present invention relates to a novel process for the industrial synthesis of perindopril in which (2S,3aS,7aS)-2-carboxyperhydroindole is esterified to protect the carboxylic group and is then condensed with N-[(S)-1-carbethoxybutyl]-(S)-alanine, and the product resulting from the condensation is then subjected to deprotection of the carboxyl carried by the heterocyclic ring. The present invention further relates to pharmaceutical dosage forms of perindopril prepared by a process according to the present invention.

(2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole-2-carboxylic acid (formula (I)), perindopril, and its addition salts, in particular the tert-butyl amine salt thereof, is known to have interesting pharmacological properties.



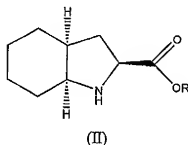
Perindopril exerts an inhibiting activity on certain enzymes, such as carboxypeptidases, enkephalinases or kinase II. In particular, perindopril inhibits the conversion of angiotensin I decapeptide to angiotensin II octapeptide, which in certain cases is responsible for arterial hypertension, by acting on the conversion enzyme.

The therapeutic use of perindopril can thus reduce or even suppress the activity of these enzymes, which are responsible for hypertensive disorder or for cardiac insufficiency.

In particular, perindopril can be distinguished from other conversion enzyme inhibitors by its intensity and duration of action.

Perindopril, the preparation thereof and its therapeutic use have been described in EP 0,049,658.

One of the starting materials which can be employed for the preparation of perindopril is (2S,3aS,7aS)-2-carboxyperhydroindole, described in EP 0,037,231, or an ester thereof, which can be represented by following formula (II)



where R denotes a hydrogen atom, lower alkyl or benzyl group.

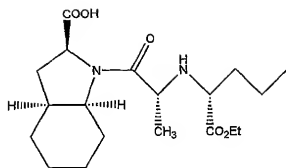
The preparation of a compound of formula (II) can be carried out by means of well-known methods described the prior art, for example above referred to EP 0,037,231, EP 0,084,164, EP 0,115,345, EP 0,173,199 and EP 0,132,580.

The starting material for the synthesis of a compound of formula (II), employed by some of the prior art processes, is 2-carboxyindole, which is readily available and relatively inexpensive (EP 0,0371,231). 2-carboxyindole is subjected to catalytic reduction over rhodium to give a mixture of the two *cis endo* isomers of (2S,3aS,7aS) and (2R,3aR,7aR) configuration respectively. However, the separation of the (2S,3aS,7aS) isomer, which can be used in the synthesis of perindopril, from the (2R,3aR,7aR) isomer generally requires the use of methods which are particularly arduous to employ.

For the synthesis of a compound of formula (II), EP 0,115,345 employs several stages requiring the esterification of the carboxylic acid group with benzyl alcohol, the conversion of the amino ester to a salt with (S)-N-benzyloxycarbonyl phenylalanine, the separation of the S,S,S isomer by fractional crystallization, and the liberation of the amino group, optionally followed by the liberation of the carboxylic acid group.

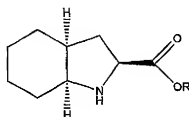
EP 0,308,341 describes the preparation of the (2S,3aS,7aS)-2-carboxyperhydroindole as the benzyl ester p-toluene sulphonate salt and its further conversion to perindopril.

The present invention now provides a process of preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof



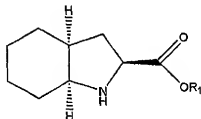
(I)

which process comprises protecting a compound of formula (II)



(II)

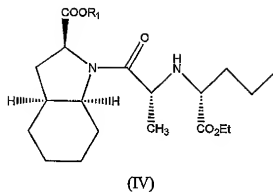
where R denotes a hydrogen atom, in the presence of benzene sulphonic acid as a catalyst, to obtain the benzene sulphonic acid salt of an ester of formula (III)



(III)

where R₁ is a carboxyl protecting group and reacting said ester of formula (III) with N-[(S)-1-carbethoxybutyl]-(S)-alanine to obtain a compound of formula (IV)

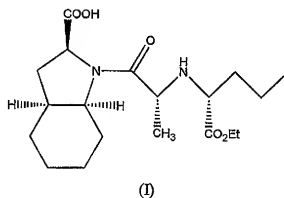
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where R_1 is as defined above; and deprotecting a compound of formula (IV) to yield perindopril of formula (I), or a pharmaceutically acceptable salt thereof.

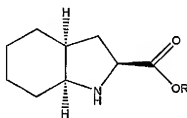
Preferably, the R_1 carboxyl protecting group is an optionally substituted aralkyl group, preferably a protecting benzyl group, suitably selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl.

In a preferred embodiment, the present invention provides a process of preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof



which process comprises the steps of:

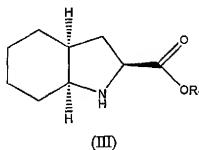
- (i) reacting a compound of formula (II)



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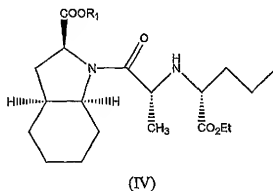
(II)

where R denotes a hydrogen atom, with a benzyl alcohol suitably selected from unsubstituted benzyl alcohol, 4-halo benzyl alcohol or 4-C₁₋₄alkoxy benzyl alcohol, in the presence of benzene sulphonic acid as a catalyst, to obtain the benzene sulphonic acid salt of a benzyl protected ester of formula (III)



where R₁ is a protecting benzyl group, suitably selected from unsubstituted benzyl, 4-halo phenylmethyl and 4-C₁₋₄alkoxy phenylmethyl;

(ii) reacting said ester of formula (III) with N-[(S)-1-carbethoxybutyl]-(S)-alanine to obtain a compound of formula (IV)



where R₁ is as defined above; and

(iii) deprotecting a compound of formula (IV) to yield perindopril of formula (I), or a pharmaceutically acceptable salt thereof.

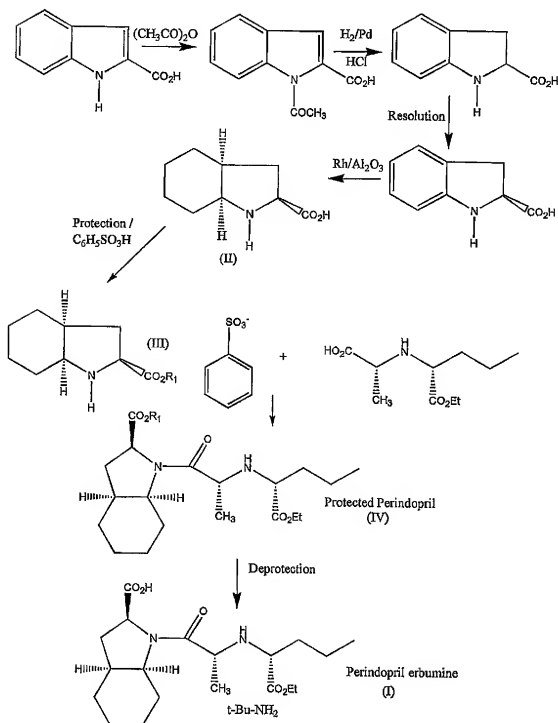
Preferably R₁ in above formulae (III) and (IV) represents unsubstituted benzyl, 4-chloro phenylmethyl or 4-methoxy phenylmethyl. As such, preferred benzyl alcohols for

reaction with a compound of formula (II) in above defined step (i) are unsubstituted benzyl alcohol, 4-chloro benzyl alcohol and 4-methoxy benzyl alcohol. Preferably, a compound of formula (II) is reacted with the benzyl alcohol, in the presence of benzene sulphonic acid, with simultaneous removal of water formed in the reaction, suitably either under Dean-Stark conditions, or by use of molecular sieves, to give after isolation the benzene sulphonic acid salt of the benzyl ester of (2S,3aS,7aS)-2-carboxyperhydroindole of formula (III), which is then reacted with N-[(S)-1-carbethoxybutyl]-(S)-alanine in the presence of N, N-dicyclohexylcarbodiimide and hydroxy benzotriazole. The benzene sulphonic acid salt of the benzyl ester of (2S,3aS,7aS)-2-carboxyperhydroindole of formula (III) is preferably basified and reacted with N-[(S)-1-carbethoxybutyl]-(S)-alanine in the presence of N, N-dicyclohexylcarbodiimide and hydroxy benzotriazole, in a water immiscible solvent, such as ethyl acetate.

It is further preferred that the benzene sulphonic acid is used in a molar ratio, or in a slight excess of the molar equivalent, with respect to (2S,3aS,7aS)-2-carboxyperhydroindole of formula (II). It is further preferred that esterification of a compound of formula (II) is carried out in a hydrocarbon solvent, such as toluene or xylene, and is typically carried out at reflux temperature for a period of 12 to 24 hours.

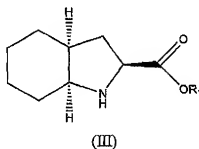
Deprotection of a compound of formula (IV) is typically carried out under mild hydrogenation conditions, suitably using palladium on carbon as the catalyst, in a water immiscible solvent, such as ethyl acetate, under alkaline or neutral conditions. Optionally, therefore, the deprotection can be carried out in the presence of an organic base. More preferably, deprotection is carried out in the presence of a base which forms a pharmaceutically acceptable salt with the free acid of perindopril formed by the deprotection and a preferred base is thus tert-butyl amine, which can be used in molar quantities with respect to a compound of formula (IV), to give after isolation, perindopril as the erbumine salt which is provided in a very pure form, with very high optical and chromatographic purity. Deprotection of a compound of formula (IV) can also be carried out with suitable oxidizing agents, such as ceric ammonium nitrate or the like. In an alternative embodiment of the invention, hydrogenation of a compound of formula (IV) is carried out using a solvent, such as an alcoholic solvent, under basic conditions, at pressures ranging from atmospheric to 50 psi for 5 to 10 hours, followed by isolation of the salt of perindopril directly from the reaction mixture. A suitable alcoholic solvent can be isopropanol.

(2S,3aS,7aS)-2-carboxyperhydroindole of formula (II) is prepared from commercially available indole-2-carboxylic acid, or an ester thereof, by a series of reaction steps, including acetylation, reduction, resolution and further hydrogenation, and an overall process according to the present invention for the preparation of perindopril erbumine can be represented by the following reaction scheme.

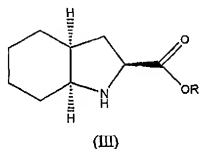


where R_1 is a protecting benzyl group, suitably selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl, and more preferably R_1 is unsubstituted benzyl, 4-chloro phenylmethyl or 4-methoxy phenylmethyl.

There is also provided by the present invention the benzenesulphonic acid salt of an ester of formula (III)

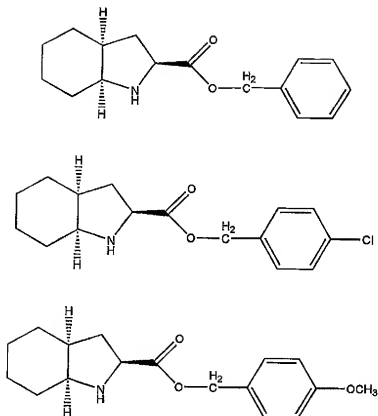


where R_1 is a carboxyl protecting group. More particularly, the present invention provides the benzenesulphonic acid salt of an ester of formula (III)



where R_1 is a protecting benzyl group, suitably selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl.

Specifically, the present invention provides benzenesulphonic acid salts of the following intermediate compounds suitable for use in the preparation of perindopril, or a pharmaceutically acceptable salt thereof



There is also provided by the present invention use of a compound of formula (III) substantially as hereinbefore described as an intermediate in the preparation of perindopril, or a pharmaceutically acceptable salt thereof.

Perindopril as provided by a process according to the present invention has therapeutic utility as an ACE inhibitor.

In addition, the present invention further provides a method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of perindopril (preferably perindopril erbumine) as provided according to the present invention.

The present invention also provides use of perindopril as provided according to the present invention (preferably perindopril erbumine) in the manufacture of a medicament for inhibiting ACE.

A patient can be in need of treatment to inhibit ACE, for example when the patient is suffering from hypertension, chronic congestive heart failure, or the like. Inhibition of ACE reduces levels of angiotensin II and thus inhibits the vasopressor, hypertensive and hyperaldosteronemic effects caused thereby. Inhibition of ACE would also potentiate

endogenous levels of bradykinin. An effective ACE inhibitory amount of perindopril as provided according to the present invention is that amount which is effective in inhibiting ACE in a patient in need thereof which results, for example, in a hypotensive effect.

In effecting treatment of a patient, perindopril as provided according to the present invention can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, perindopril as provided according to the present invention can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated and the stage of the disease.

Perindopril as provided according to the present invention can be administered in the form of pharmaceutical compositions or medicaments which are prepared by combining the perindopril according to the present invention with pharmaceutically acceptable carriers, diluents or excipients therefor, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

In another embodiment, the present invention provides pharmaceutical compositions comprising an effective ACE inhibitory amount of perindopril as provided according to the present invention (preferably perindopril erbumine), together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor. Perindopril as provided according to the present invention, including salts thereof, are typically formulated in oral dosage form of 2mg, 4mg or 8mg.

By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient must be compatible with perindopril as provided according to the present invention, and not be deleterious to a recipient thereof.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier, diluent or excipient may be a solid, semi-solid, or liquid material, which can serve as a vehicle or medium for the active ingredient. Suitable carriers, diluents or excipients are well known in the art. Pharmaceutical compositions according to the present invention may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solutions, suspensions or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, perindopril as provided by the present invention may be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups and the like.

The tablets, pills, capsules, and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose; disintegrating agents such as alginic acid, corn starch and the like; lubricants, such as magnesium stearate; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration perindopril as provided according to the present invention may be incorporated into a solution or suspension. The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; and buffers such as acetates, citrates or phosphates. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The present invention will now be further illustrated by the following Examples, which do not limit the scope of the invention in any way.

ExamplesExample 1Synthesis of (2S,3aS,7aS)-2-carboxyperhydroindole benzyl ester benzene sulphonic acid salt

10 gm of (2S,3aS,7aS)-2-carboxyperhydroindole was mixed with 7 gm of benzyl alcohol and 11.3 gm of benzene sulphonic acid in 150 ml of toluene. The reaction mixture was refluxed for 10 hours with concomitant removal of water using a Dean-Stark apparatus. After the completion of reaction, the toluene was concentrated under vacuum. To the residue was charged 100 ml of ethyl acetate. The reaction mixture was stirred for 4 hours at 20°C and the precipitated product was filtered and dried to give 19 gm of the title compound as a white solid.

Example 2Synthesis of (2S,3aS,7aS)-2-carboxyperhydroindole-4-chloro-benzyl ester benzene sulphonic acid salt

10 gm of (2S,3aS,7aS)-2-carboxyperhydroindole was mixed with 6.5 gm of 4-chlorobenzyl alcohol and 11.3 gm of benzene sulphonic acid in 150 ml of toluene. The reaction mixture was refluxed for 10 hours with concomitant removal of water using a Dean-Stark apparatus. After the completion of reaction, the toluene was concentrated under vacuum. To the residue was charged 50 ml of ethyl acetate. The reaction mixture was stirred for 6 hours at 10°C and the precipitated product was filtered and dried to give 15 gm of the title compound as a solid.

Example 3Synthesis of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole-2-carboxylic acid tert-butylamine salt

20 gm of (2S, 3aS, 7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole-2-carboxylic acid-4-chloro benzyl ester was dissolved in 200 ml of ethyl acetate. 2.5 gm of tert-butyl amine was added followed by 2 gm of palladium on carbon. The reaction mixture was hydrogenated at 40 psi for 8 hours. After completion of reaction,

the catalyst was filtered. The solvent was concentrated to 2 volume under vacuum, chilled to 5°C for 4 hours and filtered to give 14 gm of the title compound as a white colored solid.

Example 4

Synthesis of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole-2-carboxylic acid tert-butylamine salt}

5 gm of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole-2-carboxylic acid-4-methoxybenzyl ester was dissolved in 200 ml of ethyl acetate. 0.5 gm of palladium on carbon was added and the reaction mixture was hydrogenated at 40 psi for 5 hours. After completion of reaction, the catalyst was filtered. To the clear filtrate was charged 0.75 gm of tert-butyl amine and the mixture was heated at 45°C for 2 hours. The mixture was concentrated under vacuum to 2.5 volume and chilled to 5°C for 2 hours. The precipitated product was filtered and dried under vacuum to yield 3.6 gm of the title compound as white solid.

The description and examples as described above are not intended to be exhaustive or limiting of the invention. Rather, the invention is intended to cover all alternatives, modifications and equivalents included within its spirit and scope.

Example 5

Synthesis of (2S,3aS,7aS)-2-carboxyperhydroindole-4-methoxy-benzyl ester benzene sulphonic acid salt

10 gms of (2S,3aS,7aS)-2-carboxyperhydroindole was mixed with 6.5 gm of 4-methoxy benzyl alcohol and 11.3 gm of benzene sulphonic acid in 150 ml of toluene. The reaction mixture was refluxed for 10 hrs with concomitant removal of water using a Dean-stark apparatus. After the completion of reaction, the toluene was concentrated under vacuum. To the residue was charged 100 ml of ethyl acetate. The reaction mixture was stirred for 4 hours at 10°C and the precipitated product was filtered and dried to give 19 gm of the title compound as white solid.

Example 6Synthesis of (2S, 3aS, 7aS)-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole 2-carboxylic acid benzyl ester

40 gm of (2S, 3aS, 7aS)-2-carboxyperhydroindole benzyl ester benzene sulphonic acid salt was suspended in 400 ml dichloromethane. The pH of the mixture was made alkaline with aqueous ammonia. 200 ml water was added and the mixture was stirred for 30 min. Organic layer was separated and washed till neutral with water. Organic layer was dried and cooled to 10°C. 6 gm of hydroxy benzotriazole and 21.25 gm of N-[(S)-1-carbethoxybutyl]-(S)-alanine was added at 10-15°C, immediately 20.25 gm of N,N'-dicyclohexylcarbodiimide dissolved in 100 ml dichloromethane was added maintaining temperature between 10-15°C. After completion of reaction the insolubles were filtered. Organic layer was washed with saturated sodium bicarbonate followed by water, organic layer was then dried with sodium sulphate and concentrate to get oil. The resulting oil was dissolved in 200 ml diisopropyl ether and cooled to 10°C, stirred for 30 min and filtered through hyflo. Organic layer was concentrated to get 43 gm of the title compound as oil.

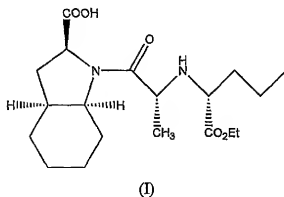
Example 7Synthesis of (2S, 3aS, 7aS)-{2-[1-(ethoxycarbonyl)-(S)-butylamine]-(S)-propionyl]-octahydroindole 2-carboxylic acid -4-chloro benzyl ester

50 gm of (2S, 3aS, 7aS)-2-carboxyperhydroindole-4-chloro-benzyl ester benzene sulphonic acid salt was suspended in 500 ml dichloromethane. The pH of the mixture was made alkaline with aqueous ammonia. 250 ml water was added and the mixture was stirred for 30 min. Organic layer was separated and washed till neutral with water. Organic layer was dried and cooled to 10°C. 7 gm of hydroxy benzotriazole and 25 gm of N-[(S)-1-carbethoxybutyl]-(S)-alanine was added at 10-15°C, immediately 24 gm of N,N'-dicyclohexylcarbodiimide dissolved in 100 ml dichloromethane was added maintaining temperature between 10-15°C. After completion of reaction the insolubles were filtered. Organic layer was washed with saturated sodium bicarbonate followed by water, organic layer was then dried with sodium sulphate and concentrate to get oil. The resulting oil was dissolved in 200 ml diisopropyl

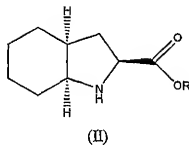
ether and cooled to 10°C, stirred for 30 min and filtered through hyflo. Organic layer was concentrated to get 50 gm of the title compound as oil.

CLAIMS

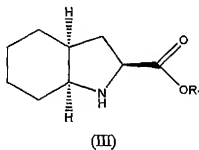
1. A process of preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof



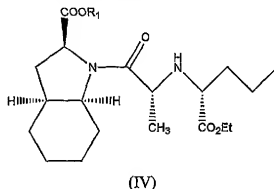
which process comprises protecting a compound of formula (II)



where R denotes a hydrogen atom, in the presence of benzene sulphonic acid as a catalyst, to obtain the benzene sulphonic acid salt of an ester of formula (III)



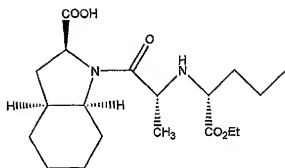
where R_1 is a carboxyl protecting group and reacting said ester of formula (III) with N-[(S)-1-carbethoxybutyl]-(S)-alanine to obtain a compound of formula (IV)



where R_1 is as defined above; and deprotecting a compound of formula (IV) to yield perindopril of formula (I), or a pharmaceutically acceptable salt thereof.

2. A process according to claim 1, wherein said R_1 carboxyl protecting group is an optionally substituted aralkyl group.
3. A process according to claim 2, wherein said R_1 carboxyl protecting group is a benzyl group.
4. A process according to claim 3, wherein said benzyl group is selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl.
5. A process according to claim 4, wherein said benzyl group is selected from unsubstituted benzyl, 4-chloro phenylmethyl and 4-methoxy phenylmethyl.
6. A process of preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof

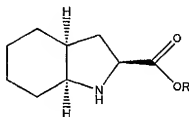
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(I)

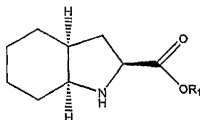
which process comprises the steps of:

- (i) reacting a compound of formula (II)



(II)

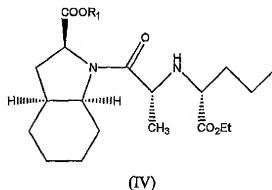
where R denotes a hydrogen atom, with a benzyl alcohol in the presence of benzene sulphonic acid as a catalyst, to obtain the benzene sulphonic acid salt of a benzyl protected ester of formula (III)



(III)

where R₁ is a protecting benzyl group;

(ii) reacting said ester of formula (III) with N-[(S)-1-carbethoxybutyl]-(S)-alanine to obtain a compound of formula (IV)



where R_1 is as defined above; and

(iii) deprotecting a compound of formula (IV) to yield perindopril of formula (I), or a pharmaceutically acceptable salt thereof.

7. A process according to claim 6, wherein said benzyl alcohol is selected from unsubstituted benzyl alcohol, 4-halo benzyl alcohol and 4- C_{1-4} alkoxy benzyl alcohol, and said benzyl protecting group is respectively selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl.

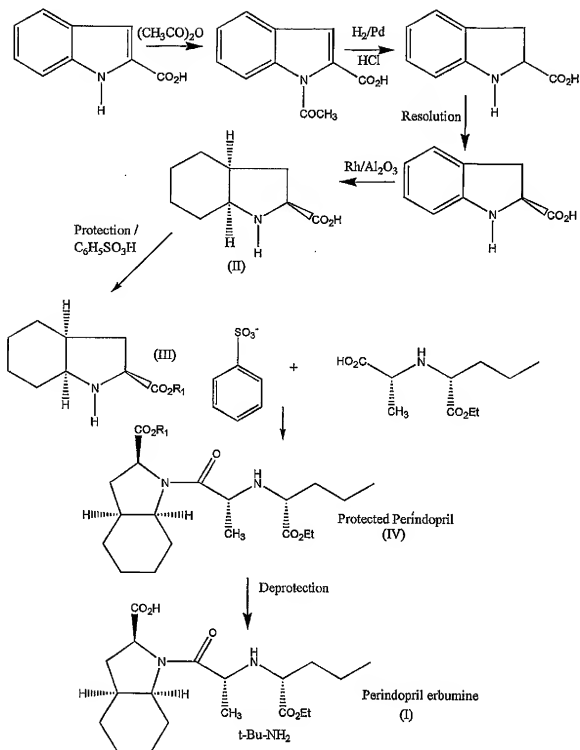
8. A process according to claim 7, wherein said benzyl alcohol is selected from unsubstituted benzyl alcohol, 4-chloro benzyl alcohol and 4-methoxy benzyl alcohol and said benzyl protecting group is respectively selected from unsubstituted benzyl, 4-chloro phenylmethyl and 4-methoxy phenylmethyl.

9. A process according to any of claims 3 to 9, wherein a compound of formula (II) is reacted with a benzyl alcohol, in the presence of benzene sulphonic acid, with simultaneous removal of water formed in the reaction.

10. A process according to claim 9, wherein water is removed either under Dean-Stark conditions, or by use of molecular sieves.

11. A process according to any of claims 1 to 10, wherein a compound of formula (III) is reacted with N-[(S)-1-carbethoxybutyl]-(S)-alanine in the presence of N, N-dicyclohexylcarbodiimide and hydroxy benzotriazole.
12. A process according to claim 11, wherein a compound of formula (III) is basified and reacted with N-[(S)-1-carbethoxybutyl]-(S)-alanine in the presence of N, N-dicyclohexylcarbodiimide and hydroxy benzotriazole, in a water immiscible solvent.
13. A process according to claim 12, wherein the water immiscible solvent is ethyl acetate.
14. A process according to any of claims 1 to 13, wherein said benzene sulphonic acid is used in a molar ratio, or in a slight excess of the molar equivalent, with respect to a compound of formula (II).
15. A process according to any of claims 1 to 14, wherein protection of a compound of formula (II) is carried out in a hydrocarbon solvent.
16. A process according to claim 15, wherein said hydrocarbon solvent is toluene or xylene.
17. A process according to any of claims 1 to 16, wherein protection of a compound of formula (II) is carried out at reflux temperature for a period of 12 to 24 hours.
18. A process according to any of claims 1 to 17, wherein deprotection of a compound of formula (IV) is carried out using palladium on carbon as the catalyst, in a water immiscible solvent, under alkaline or neutral conditions.
19. A process according to claim 18, wherein the water immiscible solvent is ethyl acetate.

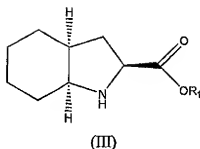
20. A process according to any of claims 1 to 19, wherein deprotection of a compound of formula (IV) is carried out in the presence of an organic base.
21. A process according to claim 20, wherein said base forms a pharmaceutically acceptable salt with the free acid of perindopril formed by the deprotection.
22. A process according to claim 21, wherein said base is tert-butyl amine which provides perindopril erbumine further to said deprotection.
23. A process of preparing perindopril, or a pharmaceutically acceptable salt thereof, represented by the following reaction scheme



where R_1 is selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl.

24. Benzene sulphonate salt of an ester of formula (III)

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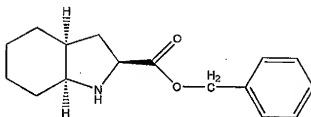


where R_1 is a carboxyl protecting group.

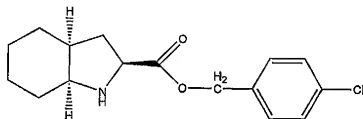
25. Benzene sulphonic acid salt of an ester of formula (III) according to claim 24, wherein R_1 is a protecting benzyl group.

26. Benzene sulphonic acid salt of an ester of formula (III) according to claim 25, wherein R_1 is selected from unsubstituted benzyl, 4-halo phenylmethyl and 4- C_{1-4} alkoxy phenylmethyl.

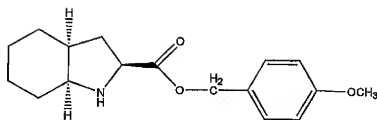
27. Benzene sulphonic acid salt of an ester of the following compound



28. Benzene sulphonic acid salt of an ester of the following compound



29. Benzene sulphonic acid salt of an ester of the following compound



30. Use of a benzene sulphonic acid salt according to any of claims 24 to 29, as an intermediate in the preparation of perindopril, or a pharmaceutically acceptable salt thereof.
31. Perindopril, or a pharmaceutically acceptable salt thereof, prepared by a process according to any of claims 1 to 23.
32. Perindopril, or a pharmaceutically acceptable salt thereof, according to claim 31, for use in therapy.
33. A method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of perindopril, or a pharmaceutically acceptable salt thereof, according to claim 31.
34. Use of perindopril, or a pharmaceutically acceptable salt thereof, according to claim 31, in the manufacture of a medicament for inhibiting ACE.
35. A pharmaceutical composition comprising an effective ACE inhibitory amount of perindopril, or a pharmaceutically acceptable salt thereof, according to claim 31, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.